The Control of Diseases of Tissue Reactivity by Cortisone

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In this paper, a review of the use of cortisone acetate in diseases of tissue reactivity is given, and particular attention is directed to the author's experience of its application to one of these diseases—psoriasis.

Pathology of Psoriasis.

The primary lesion is often a well defined pinhead size papule covered with fine silvery scales. The individual lesions spread at the periphery and often unite with other patches to form large plaques and sheets. Histological examination shows excessive growth of the epithelium with a badly formed horny layer (parakeratosis) and a downward growth of the interpapillary processes. As the patch enlarges healing and hyperparakeratosis occur behind the advancing periphery. There is a cellular infiltration around the papillary and subpapillary vessels and leucocytes collect between the horny cells.

Aetiology.

Various causes have been suggested in the past for the appearance of psoriasis —parasitic agencies, toxins of bacterial and metabolic origin, neuropathic disturbances, mechanical trauma and heredity.

Psoriasis is a "disease of tissue reactivity," that is the defensive and reparative processes (whatever the ætiological agent) in the epithelial tissues are active and the repair constitutes the visible disease. In diseases of tissue reactivity the common site of involvement is mesenchymal tissue (fibroblasts and reticulo endothelial elements), but epithelium, where repair and replacement are constantly necessary, is also affected. Numerous examples of the harmful effects of mesenchymal tissue responses to injury, both during the active stages of inflammation and repair and in the late healed stage, can be found in a clinical survey; uveitis and rheumatoid arthritis demonstrate distortion of normal morphology and disturbance of normal function in the eye and joints respectively; fibrosis with reduction of blood supply in chronic inflammatory lesions prevents immune bodies and drugs from inhibiting the growth and activity of bacteria in the inflamed area; fibrosis causes contraction and obstruction of tubes—in the œsophagus, duodenum, urethra, etc.—and distorts the heart valves in rheumatic fever. Two examples of diseases of overactivity of the repair process in the epithelial tissue group are obvious—psoriasis, with its hyperkeratosis, and keloid formation after burns or injuries.

Inflammation is basically the same after different forms of injury (Menkin, 1940); it involves the local and the general response—the latter incorporating stimulation of the pituitary and adrenal glands (Selye, 1946 and 1949). Selye has given the terms alarm reaction and adaptation mechanism to these changes.

Treatment of these diseases of tissue reactivity, different in ætiology but similar in effect, must be directed at (1) removing the causative agent, where known; and (2) the control of tissue proliferation. Several research workers have shown that the administration of cortisone acetate (a secretion of the cortex of the adrenal gland) or pituitary adrenocorticotrophic hormone, ACTH (which stimuates the production of cortical hormone), has inhibited the proliferation of mesenchymal and epithelial tissues (Baker, 1949; Becks, et al., 1944). Baker demonstrated that ACTH retards wound healing by decreasing the cellularity of connective tissue and by causing atrophy of collagen fibres, and also that it determines an atrophy of the epithelial structures—hair, epidermis and sebaceous glands. Ragan, et al. (1949) observed that ACTH and cortisone retarded fibroblast production. It appears, from consideration of various results, that the relatively large doses of cortisone given to animals retard wound healing, but the moderate therapeutic doses (100 mg. daily) given to humans have little notable effect on incidental wound healing.

Although it may not be possible to suppress the causative agent in many of these diseases, it is now obvious that the tissue proliferation and exudation may be controlled—either directly by the oral or parenteral administration of exogenous cortisone, or indirectly by the injection of ACTH, which stimulates the adrenal cortex to increase its endogenous hormone production.

Hench (1949) and his co-workers reported the suppressive effect of these hormones on the tissue reactivity of rheumatoid arthritis. In acute rheumatic fever and rheumatoid arthritis there is widespread involvement of the mesenchymal tissues characterized by focal injuries to connective tissue, with œdematous swelling and degeneration of collagen fibres. The pathological changes in the subcutaneous nodules of rheumatoid arthritis consist of foci of collagen degeneration similar to the focal changes in anaphylactic hypersensitivity. Cortisone and ACTH therapy, in patients with rheumatoid arthritis, reduced the fibrous tissue reaction and gave early relief from pain and increased the mobility of joints. Early acute cases responded best, because chronic cases showed irreversible bony and old scar tissue deformities. Laboratory control demonstrated a fall in the red cell sedimentation rate and a reduction in blood globulin. Albright (1943) has described the adrenal cortex as anti-anabolic, and it is possible that the fall of blood globulins after the administration of cortisone may be due to inhibition of protein synthesis. It is now known that the effect of ACTH and cortisone on rheumatoid arthritis is confined to a temporary suppression of activity during the period of treatment and that they have no other effect on the course of the disease (Freyberg, 1950).

In rheumatic infection the antibodies to hæmolytic streptococcal infection arise

from those mesenchymal cells (reticulo-endothelial system) which produce immune bodies, and it has been stated that these antibodies are the agents which damage the connective tissues (Gubner, 1949). The effectiveness of cortisone in acute rheumatic diseases, however, is due to direct action on the mesenchymal connective tissues and not to suppression of mesenchymal immune bodies—because in man cortisone does not inhibit antibody formation (Mirick, 1950).

Although cortisone does not inhibit antibody formation in man, a diminution of antibody response has been demonstrated in animals during its administration (Bjorneboe, 1951)—possibly due to relatively large doses. The question arises whether or not cortisone increases susceptibility to infection. Finland (1950) and co-workers treated pneumococcal pneumonia in man with ACTH and the general signs of illness were suppressed in twenty-four hours, but the blood and sputum contained type 8 pneumococci for four days; however, there was no interference with the normal antibody response. In experimental pneumococcal infection the results were unfavourable (White and Marshall, 1951). If the diagnosis between rheumatic fever and subacute bacterial endocarditis, or between non-infective and pyogenic arthritis (including tuberculosis), is doubtful, antibiotics, sulphonamides or other drugs lethal to micro-organisms should be administered before cortisone to avoid the possibility of uncontrolled bacteræmia or septicæmia.

Cortisone has also been used to depress the reaction of mesenchymal derivates in certain experimental states—for example, the tuberculin reaction (Stoerck, 1950), the Schwartzman phenomenon (Soffer, et al., 1950) and anaphylaxis (Dougherty, 1949).

The hypersensitive state—which includes anaphylaxis or serum sickness and bacterial allergy—has responded well to treatment with cortisone and ACTH.

The hypersensitive state may manifest itself as anaphylaxis (serum sickness) with degeneration of collagen and spasm of smooth muscle following injection of egg albumin or foreign serum into an animal sensitized to these proteins, or as bacterial allergy—a local inflammatory necrotising lesion succeeding the introduction of a specific antigen (for example, tuberculin) in an animal sensitized by infection with the corresponding organism (tubercle bacillus in this example). Both anaphylaxis and bacterial allergy are due to the interaction of a sensitizing antigen with the specific antibody; though fundamentally similar, the results are different and one can be established independently of the other.

During the process of developing active immunity to infection with bacteria the body tissues become hypersensitive to the protein of the attacking organisms. Subsequently, the tissues will suffer severe local damage by small amounts of the bacterial protein which are harmless to a normal body. Rich has stressed the fact that immunity and allergy are separate and distinct phenomena. Bacterial allergy may be seen in many infections—streptococcal, pneumococcal, straphylococcal, etc.

Anaphylaxis and bacterial allergy differ in that anaphylaxis can be passively transferred—that is, the serum of a sensitized animal will make a normal animal

anaphylactic, but the serum of an allergic animal will not induce allergy in a normal animal. Bacterial allergy does not depend on circulating antibody whereas anaphylaxis does. In the tuberculin type of allergic reaction the change progresses slowly over a number of days and occurs within the cells. In the anaphylactic local reaction necrosis and damage result from (1) increased permeability and necrosis of vascular endothelium and interference with tissue nutrition; (2) spasmodic contraction of smooth muscle fibres; (3) degeneration and fragmentation of collagen. There is often an associated eosinophilia in blood and tissue. Involvement of vascular endothelium gives rise to such conditions as purpura, urticaria and angioneurotic œdema; when smooth muscle is affected conditions like asthma are apparent. The pathological processes in the cells which are the seat of the reaction are not clear, but there may be released proteolytic enzymes, histamine or acetyl choline.

Many substances in addition to foreign protein are capable of producing anaphylactic hypersensitivity—simple chemical substances like iodine and more complex chemicals like atropine, sulphonamides and penicillin. The simpler substances may combine with body proteins to form more complex antigens. Carey (1950) and others proved the efficacy of ACTH and cortisone in treating patients suffering from various hypersensitivity reactions (exfoliative dermatitis after iodine therapy, angioneurotic œdema and urticaria after penicillin, and dermatitis and leucopenia following sulphonamide treatment, etc.).

There is reason to believe that the anaphylactic type of hypersensitivity may be the cause of the pathological changes in more diseases than those mentioned in the two preceding paragraphs. Weintraud (1913) and later investigators have suggested that the focal lesions of rheumatic fever are due to anaphylactic responses to bacterial products released in the tissues of patients who have been sensitized by infection. Rich (1943) demonstrated in rabbits sensitized to sterile horse serum, with anaphylactic sequelæ, lesions similar to those of human rheumatic carditis. He further showed vascular lesions of periarteritis nodosa following anaphylactic hypersensitivity to serum and sulphonamides. He emphasised the importance of remembering that both anaphylactic hypersensitivity and the tuberculin type of hypersensitivity may develop during bacterial infection. For example, in pneumococcal infection the capsular carbohydrate induces anaphylactic hypersensitivity and the somatic protein causes the tuberculin type of hypersensitivity. The two hypersensitive states may occur in infection with hæmolytic streptococci, e.g., Coburn noted in the skins of rheumatic patients such responses as the immediate wheal and erythema.

The areas of focal damage to connective tissue elements (œdema and degeneration of collagen fibres) in acute rheumatic fever are essentially similar in microscopic appearance to the tissue damage in local anaphylaxis (including the Arthus phenomenon). Rich also emphasised the presence of that criterion of local anaphylaxis, tissue eosinophilia, in myocarditis of rheumatic origin.

Harvey (1950) and his associates administered cortisone and ACTH to

patients suffering from ocular diseases in which hypersensitivity played a part and found dramatic improvement; the cortisone and ACTH blocked the inflammatory and exudative manifestations. These diseases were non-granulomatous iritis (a manifestation of bacterial hypersensitivity), sympathetic ophthalmia (hypersensitivity to uveal tract pigment), and tuberculous uveitis (hypersensitivity to tuberculo—protein).

Woods and Wood (1950) demonstrated experimentally in rabbits that cortisone and ACTH reduced or abolished the inflammatory and exudative phase of the ophthalmic reaction in bacterial allergy, the ocular protein anaphylactic reaction, the focal lesions in tuberculous eyes and the non-hypersensitive reaction to irritants (glycerine and jequirity infusions) instilled into the conjunctiva. The last experiment—blocking of the non-hypersensitive reaction to chemcial irritation—is evidence that cortisone acts directly on the mesenchymal tissues and not on the antigen-antibody reaction.

In diseases where the hypersensitive state is due to invading organisms the treatment must not be confined to a reduction by cortisone in tissue damage, but must include an attack on the virulent organisms by antibiotics, sulphonamides or other specific forms of therapy. Since cortisone cannot be used indefinitely, its beneficial effects are greatest in those hypersensitive states which have a limited duration or in which the infection can be quickly overcome.

It has been stated that cortisone has an anti-hyaluronidase action. Hyaluronidase, the spreading factor of Duran-Reynals (1942), is an enzyme which lowers the viscosity of hyaluronic acid to that of water. Hyaluronic acid, a secretion of connective tissue cells, is the ground substance of the tissue spaces and the precursor of collagen. The spreading factor can be extracted from invasive bacteria such as staphylococci, pneumococci, and streptococci, from testicular and malignant tissues and from snake venom.

Turner and Hollander (1950), in a paper on the effect of cortisone in experimental syphilis in rabbits, noted that the syphilomas were small, contained a tenacious mucoid material (hyaluronic acid) and exhibited a paucity of mononuclear cells; virulent treponemes multiplied more rapidly than in control experiments where no cortisone was administered. When cortisone and penicillin were given together the treponemes were killed rapidly, but the dead micro-organisms were not removed as quickly as in lesions in animals receiving penicillin only.

Carey (1950) noted a rise in leucocyte count on the third day during treatment of sulphonamide hypersensitivity with ACTH. Experimental studies have also demonstrated a marked neutrophilia with both ACTH and cortisone.

It has been reported that the increased level of circulating adrenal steroids after ACTH administration inhibits histamine formation and accelerates its breakdown. However, intracutaneous injections of histamine have been given to patients under treatment with ACTH for a variety of diseases and in no case was there any evidence that the local cutaneous reaction was suppressed. Cortison and ACTH produce remissions in asthma, but it appears that the beneficial action of the

hormones is not through an anti-histamine action—in fact, the site of operation and mechanism of the action is not yet known (Carey, 1950).

The excretion of urinary adrenal corticoids is increased in acute emotional stress, acute trauma, surgical wounds, physical strain of short duration and pregnancy. In prolonged stress or trauma there is a fall of urinary corticoids and the nitrogen loss characteristic of acute trauma is absent. It now appears that the adrenal cortical hormones mobilize protein, but the fate of the protein depends on the state of the body as a whole—in acute stress it is deaminated and lost while in chronic stress and pregnancy (where it passes to the anabolic area of fœtus and uterus) it is retained. The body state may also determine whether or not wound healing will be retarded when the level of circulating steroids is high.

It has been suggested (Selye, 1949) that there is some degree of antagonism in the body between the two groups of adrenal cortical hormones, the mineralocorticoids (e.g., desoxocortisone) and the glucocorticoids (e.g., cortisone). Selye states that the mineralocorticoids induce various defensive tissue reactions (augmentation of granuloma formation and of allergic responses, primarily in connective tissue, and anabolism). He also claimed that periarteritis nodosa, malignant nephrosclerosis and morphological changes similar to hypertensive and rheumatic diseases could be produced experimentally by administration of the mineralocorticoids desoxocortisone and desoxycorticosterone acetate.

On the contrary the glucocorticoid cortisone and ACTH (which is predominantly a glucocorticotrophic hormone) have an inhibitory effect—diminution of granuloma formation and of allergic response, inhibition of mitosis in cells (Green, 1951) and catabolism. Their suppressive effect on collagen diseases and hypersensitive states has already been described.

Toxæmia of pregnancy, in part at least, may be due to excessive secretion of mineralocorticoids and relative deficiency of glucocorticoids. Recent work points to hyperactivity of the adrenal gland in late pregnancy (Venning, 1946) and a high urinary level of mineralocorticoids in toxæmia of pregnancy (Tobian, 1949). Moore and co-workers (1951) decided on the exhibition of cortisone (despite its salt and water retaining propensities) in a series of eight cases of pregnancy toxæmia. The clinical results were good—headache was relieved, vision improved, the patients felt better, and œdema and albuminuria were reduced (though ascites appeared in some cases), but the effect on blood pressure was disappointing. It seems probable that some cortical steroids may exert a direct influence on water excretion independent of electrolytic or vascular changes.

Other effects of cortisone administration are :—

(a) Cushingoid side effects—associated with increased glucocorticoid excretion in the urine. Osteoporosis may cause fractures.
(b) Diminution of pituitary adrenocorticotrophic hormone—hence its beneficial action in the hypercorticism of the adrenogenital syndrome.
(c) Transient hypocorticism following cessation of cortisone therapy.

A test, based on the decrease in circulating eosinophile cells within a few hours

after injection of ACTH, has been devised (Thorn, et al., 1948) to diagnose Addison's disease (adrenal cortical insufficiency) or pituitary deficiency. In this test a single intramuscular injection of 25 mg. of ACTH is given, and a fall of 50 per cent. or more in the value of circulating eosinophile cells four hours later indicates a satisfactory adrenal cortical response.

The description "diffuse collagen disease" (Klemperer, et al., 1942) has been applied to several diseases of varied manifestations, but common involvement, the connective and vascular tissues. They are characterized microscopically by a general or local vasculitis, thickening of the collagen fibres and swelling of the ground substance; the terminal picture is often one of fibrinoid degeneration and necrosis. There is frequently ocular involvement in these diseases—both of the blood vessels, as in periarteritis nodosa and cranial arteritis, and of the mesenchymal tissues of the conjunctiva, iris, sclera and choroid as in rheumatoid arthritis and dermatomyositis.

The following list summarizes the diseases which respond with varying degrees of success—some of them dramatically—to treatment with cortisone and ACTH. It has been divided into groups, but grouping is obviously unsatisfactory because, for example, periarteritis nodosa is classified under "diffuse collagen diseases," and drug rashes under "hypersensitivity state"—yet it is known that hypersensitivity to iodine can produce both periarteritis nodosa and a skin rash.

Diffuse collagen diseases :

Rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis, temporal or cranial arteritis, thromboangiitis obliterans, serum sickness, scleroderma, Schönlein-Henoch purpura.

Acute inflammatory skin diseases :

Psoriasis, pemphigus, exfoliative dermatitis.

Acute inflammatory eye diseases :

Keratitis, iritis, choroiditis, uveitis, optic neuritis, conjunctivitis, sympathetic ophthalmia.

"*Hypersensitive States*" :

Angioneurotic œdema, bronchial asthma, drug rashes.

Blood disorders :

Acute leukæmia, chronic lymphatic leukæmia, Hodgkin's disease, lymphosarcoma.

Nephrotic syndrome :

Ulcerative Colitis :

Gout :

Adrenal Cortical Hormones.

The cortex of the adrenal gland secretes three types of hormones.

(a) Compound F like hormones.

(17—Hydroxycorticosterone steroids).

These hormones convert glucose to glycogen in muscles and liver and restore glycogen that has been used in the reaction to sudden stress or the "alarm" reaction; mobilize fat as a source of energy; mobilize amine acids from tissue

proteins—partly for providing energy and for conversion to glucose and glycogen and partly for protein synthesis in damaged tissues. When the compounds are administered in large doses the following changes are noted :—(1) increased excretion of nitrogen, potassium, phosphate and calcium; (2) hyperglycæmia and glycosuria; (3) decreased respiratory quotient. Cortisone acetate (11-dehydro-17 hydroxycorticosterone-21-acetate) belongs to this group.

(b) Desoxycorticosterone hormones.

An excess of circulating hormones of this group causes retention of sodium, chloride and water, increased excretion of potassium, fatigue and electrocardiographic changes. Oedema is evident due to water retention. The hormones of group A (17 hydroxycorticosterone steroids) also produce these electrolytic changes but in a less marked degree.

(c) Adrenal androgens.

When stimilated to excess secretion they result in masculinization, amenorrhœa and hirsutism. They are anabolic in character.

Treatment with Cortisone or ACTH.

The following procedure should be adopted in a full clinical and physiological investigation :—

(1) Restrict sodium chloride and increase potassium intake to avoid œdema.
(2) Record body weight daily—and, if practicable, fluid intake and output.
(3) Read blood pressure values daily, because hypertension may occur from water retention.
(4) Examine blood films for fall in eosinophile counts.
(5) Test urine for sugar.
(6) Take electrocardiograms twice weekly.

Dosage With Cortisone (Merck).

The dosage for psoriasis—at any rate for early acute cases of psoriasis—is probably comparable to that for acute rheumatoid arthritis. When a maximal response is required for early acute rheumatoid arthritis the advised dosage is :—

100 mg. every 8 hours for 3 doses; then
100 mg. every 12 hours for 2 doses; then
100 mg. every 24 hours for 7 to 14 days.

After that the daily dose should be gradually reduced (by 10 mg. every second day) until the daily dose is 50 mg. The dosage schedule may then be altered to 100 mg. every other day and this is maintained until the end of the course—which may extend up to six weeks and involve the use of up to 4 grammes of cortisone. A rest period of at least four to six weeks is allowed between each course. If the expected response is not obtained four or five days after initiating the treatment the dosage should be increased to 100 mg. every 12 hours for 4 doses. Injections must be given into muscle. Cortisone can also be given orally.

In the case treated by the author, the psoriasis was widespread and chronic and the total dose of cortisone acetate was small, 1.5 grammes. It was obvious that no dramatic response would be obtained—as in early acute rheumatoid arthritis

on full dosage—but it was hoped that the process of reversal of the pathological changes would be sufficiently established to prove the efficacy of treatment by cortisone. The results (described later) indicated that cortisone treatment was satisfactory—in that it initiated the desired regressive changes in the lesions, and because the degree of regression—incomplete though it was—was consistent with the small dosage and the long duration of the disease.

Dosage With Adrenocorticotrophic Hormone (ACTH).

This hormone from the anterior part of the pituitary gland acts by increasing the production of the adrenal cortical steroids. The aim of the treatment, as with the direct introduction of cortisone into the body, is to gain a therapeutic effect with minimum metabolic disturbance. After the disease has been suppressed the smallest effective maintenance doses are employed.

In most cases injections of 10 to 25 mg. every six hours of ACTH (Armour) are required to effect remissions in diseases like rheumatoid arthritis. Unlike cortisone, ACTH must be given at short intervals (every six hours). If the total daily dose is given in only one or two injections the response is absent or poor. The injections, as with cortisone, must be given by the intramuscular route. Usually 12.5 mg. every six hours for two weeks is sufficient to establish remission, then the dose is tapered off.

Cortisone and ACTH have recently been used in America by Freyberg (1950) and Hench in the treatment of psoriatic arthritis; they concluded that long standing cases do not respond fully even with large doses. In early cases of psoriatic arthritis, the arthritis responded to relatively small doses (10 mg. every six hours) of ACTH, but in chronic cases the arthritic response was poor even with large doses. The psoriatic lesions, in contrast with the arthritic lesions, seem to require much larger doses to effect complete remission—doses of 25 mg. or even 50 mg. every six hours have been needed. Even with these large doses the skin lesions in chronic cases do not disappear completely.

Gubner (1951) describes the suppressive effect of aminopterin (a folic acid antagonist) in diseases of reactivity—rheumatoid arthritis and psoriasis—and demonstrates striking remissions in psoriasis. However, the toxic effects were also marked, e.g., ulceration of the mouth and abdominal cramps due to suppression of normal epithelial growth in the mouth and intestinal tract, and alopecia. Gubner states that the therapeutic and toxic doses are so close as to preclude its clinical use.

Case Report.

The patient, a man of 40 years of age, had widespread psoriasis covering his back, chest, abdomen, arms and legs. He has never been free from psoriasis for the past twenty-two years, and the present widespread condition has existed for the past fifteen years. He has had relief for short periods (up to two months) on various occasions by using ultra violet light and tar ointment and stated that if he attacked one area (e.g., back or chest or arms) vigorously for fourteen to twenty-one days with the combined light and tar methods, he could restore the

skin of the selected area to normal and that the remissions would persist for four to eight weeks. His method involved using tar ointment night and morning every day and irradiation with the mercury vapour ultra violet lamp every second day; the lamp was usually placed fifteen inches from the skin and the period of irradiation was one minute on each occasion. During restoration to normal, there appeared erythema of skin and desquamation of the scales, then brown discoloration, and finally, a normal flat appearance where the former raised, red, scaly patches existed. Lately dithranol ointment gave better results than tar ointment.

He has suffered from hay fever every year. He also complained of lumbago and sciatica, and these rheumatic affections have troubled him for the past three months. X-ray examination of the lumbar spine, sacrum, coccyx, pelvis, sacro-iliac joints and intervertebral spaces showed no abnormalities. Wassermann reaction was negative. Examination revealed no cardiovascular disease, nephritis or metabolic disorder (e.g., diabetes).

Family History.

Various members of his family have had psoriasis; three brothers have intermittently had small lesions; his daughter had fleeting small psoriatic papules; his paternal grandmother complained of the same condition. His elder brother, like himself, suffered from hay fever, but his father has been free of psoriasis and hay fever.

Treatment of the Case with Cortisone.

The course consisted of 1,500 mg. (1.5 grammes) of cortisone acetate (Cortone, Merck) given by intramuscular injection over a period of fourteen consecutive days. He received 100 mg. once daily except on two days, when he got 100 mg. morning and evening, and the thirteenth and fourteenth days when he got 50 mg. each day.

During the first week of treatment he spent most of each day in bed but returned to work during the second week. He stopped all other forms of treatment, but from the seventh day used the sun lamp and tar on his right thigh, and tar ointment only on his right arm. Baths were taken as usual.

His weight was taken each day and varied from 13 stones 4 lbs. to 13 stones 6 lbs. over the course of fourteen days' treatment. It varied between 13-4lbs. and 13-5 lbs. during the first four days, then rose to 13-6 lbs., and remained at this level from the fifth to the eleventh day, when slight œdema appeared in the right ankle. Oedema with slight pitting on pressure appeared on the left ankle on the following (twelfth) day. The weight fell to 13-5lbs. on the twelfth, thirteenth and fourteenth days.

The blood pressure was recorded every second day until œdema appeared, then each day after that manifestation of electrolytic change. The readings were :—

110	115	120	120	120	120	100	100	100
85	90	90	90	90	90	75	75	75

It is evident that both the systolic and diastolic pressures rose from the initial values $\frac{110}{85}$ to $\frac{120}{90}$ on the fifth day and remained at that value until œdema appeared on the eleventh day. On the following and subsequent days, when œdema was still present, the systolic and diastolic pressures fell to below their original levels—that is, to $\frac{100}{75}$.

Retention of sodium, chloride and water with œdema may occur early in the course, but is usually followed by spontaneous diuresis on continued administration—or as a result of stopping treatment.

Blood pressure and weight rise when sodium, chloride and water retention occur, hence the increase in weight and elevation of pressure on the fifth day. The fall in body weight and blood pressure on the twelfth day may have been due to spontaneous diuresis about this time. There is also the possibility that the slight terminal hypotension was due to increased urinary excretion of potassium. No doubt the electrolytic disturbance with fluid retention was present in the body from the fifth day although it only became evident in the ankles on the eleventh day and that coincided with the spontaneous diuresis and reversal towards normal. The œdema of ankles subsided on the second day after cessation of the treatment.

The patient stopped using table salt from the beginning of the course and used salt-free foods (as far as possible) after the appearance of œdema in his legs on the eleventh day. He experienced a feeling of well-being and mental ease throughout the course of injections. This was not merely due to absence from work and business worries, because it persisted throughout the second week when he returned to his business. He mentioned on the third and eighth days that he felt thirsty.

From the third day he noted that the psoriasis had stopped burning and itching and that there was a slight decrease in the redness of some of the patches, especially on his neck. From the eighth day the psoriatic lesions were paler in the centre, the large crusts and scales had ceased to form and only fine scales were visible. At the end of the course the lesions showed definite improvement, though not complete disappearance; the centres of many lesions were paler and any scales which formed were of a fine powdery type. The right thigh and the right arm, subjected also to ultra violet light and tar inunctions, showed a more advanced improvement.

The lumbago and sciatica varied from day to day during the course and on some days symptoms had almost disappeared. At the end of the course he complained of some slight pains in the ankles.

Three weeks after the termination of the course of treatment the psoriasis showed a return to its former state—crusting had reappeared in the form of large scales, and he felt burning, itching and tightness of the skin.

Summary and Conclusions.

Cortisone acetate is a crystalline substance elaborated by the cortex of the adrenal gland; its production is stimulated by the adrenocorticotrophic hormone of the anterior part of the pituitary gland. It was originally named compound E (also independently described as substance FA and compound F) and was extracted from beef adrenal glands. Later it was synthesized from a bile acid.

The administration of cortisone is beneficial in the "diseases of tissue reactivity," that is, the collagen diseases (e.g., acute rheumatic fever and acute rheumatoid arthritis), where it suppresses fibroblastic activity and the epithelial diseases (e.g., psoriasis), where it induces remissions by inhibiting excess epithelial proliferation.

During treatment with cortisone there is suppression of inflammatory and exudative responses, but there is no attack on the factor causing the individual disease. Cortisone therefore does not cure the disease—it suppresses the proliferative activity of the host tissues and effects a disappearance of the pathological lesions during the period of administration and for a few weeks after cessation of treatment. The remission is temporary and the visible signs of disease return—unless the disease has run its course or the organisms responsible have been killed by antibiotics, sulphonamides or other means. The suppression of connective tissue proliferation reduces ultimate morphological distortion and allows therapeutic agents to enter chronic inflammatory areas and destroy embedded noxious organisms. Cortisone is palliative rather than curative.

The aim of treatment with cortisone and ACTH is to gain a therapeutic response with minimum metabolic disturbance, and when the signs of disease have gone the smallest effective dose should be employed. On account of the metabolic changes (especially those involving blood sugar levels and tissue fluid exchanges) and psychological alterations, the following conditions have been cited as contra-indications to cortisone therapy :—Hypertension, congestive heart failure, psychosis, chronic nephritis, diabetes, Cushing's syndrome and recent surgical wounds. The total dosage of cortisone in a course is three to four grammes and the course lasts two to six weeks. The standard dose is 100 mg. once daily by intramuscular injection for fourteen days, but 100 mg. may be given twice or three times daily for the first day or two. After fourteen days the daily dose is reduced by 10 mg. every second or third day, until 50 mg. daily is being given; then 100 mg. are given every other day.

In the case reported in this paper—widespread chronic psoriasis of twenty-two years' duration—the total amount of cortisone available was small (1.5 grammes) and the duration of treatment was short (fourteen days), yet there was a definite though slight improvement. The improvement manifested itself in the following changes—pallor of the central parts of the lesions, cessation of burning and itching, and the conversion of large scales and crust into fine powdery scales. These changes indicate reversal of the pathological processes in the skin and point to a more dramatic response in early acute psoriasis—when cortisone becomes more plentiful.

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REVIEW

GOOD HEALTH WITH DIABETES. By Ian Murray and Margaret B. Muir. Edinburgh: E. & S. Livingstone Ltd., 16 and 17 Teviot Place. Price 2s.

THIS booklet of forty-four pages is full of most useful hints for diabetics. In general, it contains little which can be adversely criticised. In detail, however, the authors condone the measurement of diet by eye rather than by weighing, although they suggest that weighing should be occasionally used to ensure that the eye is not becoming over-generous in its estimate. No reference is made to globin insulin.

The booklet should be helpful particularly to the newly diagnosed diabetic, as it contains the answers to many simple questions which are all too often neither answered nor anticipated by the non-diabetic medical adviser.

C. R. M.